Development of Sensors to Monitor Stroke Patients

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In the United States, approximately 550,000 new cases of stroke are reported annually, resulting in 150,000 deaths and leaving 300,000 survivors disabled. Thromboembolic strokes account for an estimated 300,000-400,000 of the 550,000 reported new cases of stroke each year. These thromboembolic strokes may be treatable by thrombolytic therapy which involves injecting a thrombolytic agent directly into the thrombus. As the clot dissolves, it breaks into fragments. One particular diagnostic fragment is the D dimer fragment which has antigenic properties. At LLNL, we are developing various catheter-based microtools to treat stroke. As part of the package, fiber optic pH sensors and D dimer biosensors are being developed for novel applications, in that they will be coaxially threaded through a catheter to the damaged area of the brain. The pH sensor would allow local measurements of tissue viability, providing an assessment on the patient's status and indicating the optimal treatment plan. The D dimer biosensor would allow local measurements of the products of thrombolysis, i.e., D dimer, assisting in the identification of clot type and providing feedback on the dosage and infusion rate of the thrombolytic agent.

The fiber optic pH sensor design was based on the immobilization of a pH sensitive dye, seminaphthorhodamine-1 carboxylate (SNARF-1C), onto the end of a 125 µm silica optical fiber using the sol-gel method. The fiber optic D dimer biosensor was based on the immobilization of D dimer monoclonal antibodies with a fluorescein isothiocyanate (FITC) label onto the end of a 125 µm silica optic fiber also using the sol-gel method.

A ratiometric-based measurement system was used for each sensor. Excitation was provided by a xenon halogen lamp with appropriate filters. The light was chopped and coupled to an optical fiber. The fluorescence was appropriately filtered and coupled to photodiodes. The photodiodes and chopper control were interfaced to lock-in amplifiers which were interfaced to a computer.

Figure 1 shows an approximately linear response of the pH sensors when the SNARF-doped fiber tips were immersed in human plasma and in human whole blood. The pH of the plasma and blood was changed by the additions of HCl and NH_40H. The fiber optic pH sensor demonstrated a fairly linear response from 6.5 to 8.5 when immersed in plasma solutions while a linear response was noted from 7.0 to 7.6 in whole blood. .Studies are underway to expand the pH sensor's performance in whole blood.

Figure 2 shows the quenching of FITC fluorescence when the D dimer antibodies and antigens combined. Initially, the fiber tip was placed in a D dimer-free phosphate buffer solution (PBS). A (+) D dimer antigen control was then added to the PBS. The concentration of D dimer antigen in PBS was 5 µg/ml which is the minimum detection level in standard *in vitro* diagnostic D dimer test kits. The fiber optic D dimer biosensor demonstrated a response when in the presence of D dimer antigens. Initial indications are however that the D dimer sensor is not completely reversible. This could be due to the high affinity between the D dimer antibodies and antigens. Studies are underway to improve the reversibility of the D dimer biosensor.

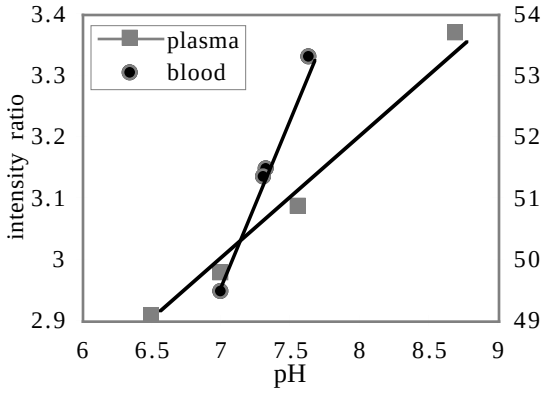

Figure 1. Fiber optic pH sensor response

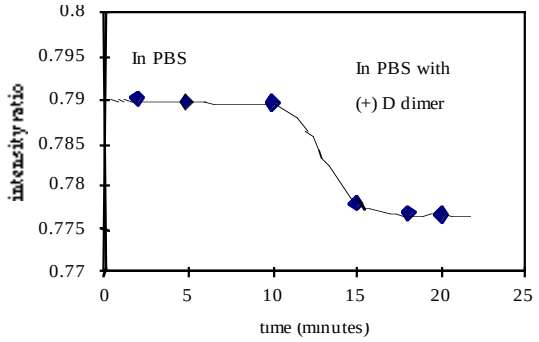

Figure 2. Fiber optic D dimer biosensor

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